Appendix Table E99. Results from studies assessing the ability of PFA-100 to predict major adverse cardiovascular events in patients with ischemic heart disease

| **Author, year**  **UID**  **Country**  **Study name** | **Treatment** | **Phenotypic Test Used [index test]** | **Clinical Outcome** | **Outcome Definition** | **Timing of measure- ment** | **Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP** | **Outcome status (e.g., bleeding or no bleeding)** | **No. with out- come status within pheno- type group** | **Comparative metric (OR, RR, HR)** | **95% CI** | **P (between which groups?)**  **[statistical test]** | **Adjusted?**  **[YES, NO, NR]**  **If YES, for what factors?** | **Procedures for multiple compari- sons [YES, NO, NR]** | **Comments (e.g., additional data in figures)** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Foussas, 2007  17892990  Greece  None | 300 or 600 mg LD and 75mg MD Clopidogrel + 100-325 mg/day aspirin | PFA-100 | Composite of cardiac death and rehospitalization for nonfatal MI | Composite of cardiac death and rehospitalization for nonfatal MI | 1 yr | Nonresponder | Composite of cardiac death and rehospitaliza-tion for nonfatal MI | 18.7% | HR= 2.7 | 1.6-4.5 | <0.001 non-responder vs. responder (Cox regression) | No | NR | NONE |
|  |  |  |  |  |  | Responder |  | 7.6% |  |  |  |  |  |  |
|  | 300 or 600 mg LD and 75mg MD Clopidogrel + 100-325 mg/day aspirin | PFA-100 | Composite of cardiac death and rehospitalization for nonfatal MI | Composite of cardiac death and rehospitalization for nonfatal MI | 1 yr | Q1 of CEPI-CT (shortest time, least responsive) | Composite of cardiac death and rehospitaliza-tion for nonfatal MI | 18.7% | HR= 3.7 | 1.8-7.5 | <0.001 Q1 vs. Q4,for HR and for trend across this and next 3 rows |  |  |  |
|  |  |  |  |  |  | Q2 |  | 12.7% |  |  |  |  |  |  |
|  |  |  |  |  |  | Q3 |  | 5.6% |  |  |  |  |  |  |
|  |  |  |  |  |  | Q4 (most responsive) |  | 5.9% |  |  |  |  |  |  |
|  | 300 or 600 mg LD and 75mg MD Clopidogrel + 100-325 mg/day aspirin | PFA-100 | Composite endpoint | Composite endpoint |  | Nonresponders | Composite endpoint |  | HR =2.9 | 1.7-3.9 | <0.001 among pts with CK-MB data, (multivariate regression) | YES; Table 4 |  |  |
|  |  |  |  |  |  |  |  |  | HR= 2.5 | 1.6-3.8 | <0.001 among all pts, (multivariate 2.5 regression) | YES; Table 5 |  |  |
| Smit, 2010  20889993  Netherlands  ON-TIME-2 | Clopidogrel 300 mg LD + 75 mg MD | PFA-ADP | MACE | mortality, urgent target vessel revascularisation or recurrent myocardial infarction | 30 days | Quartile 1 | MACE | NR | NR | NR | 0.035; between all quartiles  [Chi-square] | NO | NR | Data in figures only shows percentages; needs to be digitized to obtain accurate values |
|  |  |  |  |  |  | Quartile 2 |  | NR |  |  |  |  |  |  |
|  |  |  |  |  |  | Quartile 3 |  | NR |  |  |  |  |  |  |
|  |  |  |  |  |  | Quartile 4 |  | NR |  |  |  |  |  |  |
| Malek, 2007  17295159  Poland  NR | Clopidogrel LD 300 or 600mg and maintaining 75mg daily | PFA-100 | Early cardiovascular events | in-hospital re-infarction, cardiac arrest, recurrent angina with changes in electrocardiogram characteristic for acute ischaemia, stroke, ventricular and supraventricular arrythmias requiring electrical cardioversion or intravenous infusion of antiarrythmic drugs, pulmonary oedema, cardiogenic shock or major bleeding | Early cardiovascular events | Group 3 vs control | Early cardiovascular events | RR=9.0 | 2.4-33.9 | NR | <0.005 comparing group 3 vs control | NR | NR |  |
| Huczek, 2008  18301358  Poland  NR | Clopidogrel 75 mg | Combination of CT-EPI and CT-ADP by PFA-100 | MACE | cardiovascular death, nonfatal reinfarction, stroke, and rehospitalization for congestive heart failure | 6 months | Group I (complete platelet function inhibition) | MACE | 2 | HR=3.8  HR=1.6 | 2.2‑6.8  0.9-4.1 | P<0.0001  Groups II & III vs I  [Cox regression]  P=0.082  (group III vs II)  [Cox regression] | YES;  age, sex, treatment delay, diabetes, previous MI, chronic aspirin therapy, acute heart failure (Killip >I), anterior STEMI, culprit lesion located in the left anterior descending (LAD) artery, threevessel disease in angiography, abciximab administration, and baseline ejection fraction | NR |  |
|  |  |  |  |  |  | Group II (partial platelet function inhibition) |  | 5 |  |  |  |  |  |  |
|  |  |  |  |  |  | Group III (no platelet function inhibition). |  | 20 |  |  |  |  |  |  |
| Moerenhout, 2010  20211306  Belgium  NR | aspirin 160 mg LD + 450 mg LD of clopidogrel + Clopidogrel 75 mg MD x 6 weeks to 6 months | PFA-100 | major thrombotic adverse cardiac events (MACE) | death, nonfatal myocardial infarction  (MI), and stent thrombosis\* | 6 months | nonresponder (PFA value <71 seconds) | MACE | 2/17 (12%) | OR=2.6 (calculate) | 0.5-12.8 | P=0.2  (between nonresponder and responder)  Chi Square test | NO | NR |  |
|  |  |  |  |  |  | responder (PFA value >71 seconds) |  | 11/225 (5%) |  |  |  |  |  |  |
|  | aspirin 160 mg LD + 450 mg LD of clopidogrel + Clopidogrel 75 mg MD x 6 weeks to 6 months | PFA-100 | major thrombotic adverse cardiac events (MACE) | death, nonfatal myocardial infarction (MI), and stent thrombosis | 6 months | nonresponder (PFA value <71 seconds) | MACE | 2/17 (12%) | OR=13 | 0.9-183 | P=0.057  (between nonresponder and responder)  [Logistic regression] | YES;  sex, age, height, weight, cholesterol level, arterial hypertension, diabetes status, use of statins, use of angiotensinconverting enzyme inhibitors, multivessel disease, lesion length, total stent length, number of stents, balloon to reference ratio, post-PCI diameter stenosis, contrast dose, maximum balloon inflation pressure, balloon inflation duration, platelet count, procedural ACT, and clopidogrel nonresponsiveness. | NR |  |
|  |  |  |  |  |  | responder (PFA value >71 seconds) |  | 11/225 (5%) |  |  |  |  |  |  |
| Breet , 2010  20179285  Netherlands POPULAR | maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily | PFA-100 | Death combined | All-cause death, nonfatal MI, stent thrombosis and stroke | 1-year | High OTPR  ≤147 s | Death combined | 33/262  (12.6) | AUC: 0.5  Sens: 0.7  Spec: 0.384 | 0.46-0.55  0.585-0.795  0.35-0.42 | NR | No | NR |  |
|  |  |  | Death combined | All-cause death, nonfatal MI, stent thrombosis and stroke | 1-year | High OTPR  ≤147s | Death combined | 49/506  (9.7) | OR=1.46 | 0.85-2.48 | 0.17 high OTPR vs. normal  logistic regression | No | NR |  |
|  |  |  |  |  |  | Normal  OTPR  >147 |  | 21/306  (6.9) |  |  |  |  |  |  |
|  |  | Innovance PFA P2Y | Death combined | All-cause death, nonfatal MI, stent thrombosis and stroke | 1-year | High OTPR  ≤159 secs | Death combined | 33/262  (12.6) | AUC: 0.56  Sens: 0.391  Spec: 0.762 | 0.5-0.62  0.264-0.535  0.724-0.796 | NR | No | NR |  |
|  |  |  | Death combined | All-cause death, nonfatal MI, stent thrombosis and stroke | 1-year | High OTPR  ≤159 secs | Death combined | 18/147  (12.2) | OR=2.06 | 1.1-3.84 | 0.02 high OTPR vs. normal  logistic regression | No | NR |  |
|  |  |  |  |  |  | Normal  OTPR  >159 secs |  | 28/441  (6.3) |  |  |  |  |  |  |
| Gori, 2008  19132241  Italy RECLOSE | 600mg LD and 75mg/day MD Clopidogrel + 325 mg aspirin | CEPI PFA-100 | Stent thrombosis or cardiac death (composite) |  |  | residual platelet reactivity RPR (n=133) |  | 10 | NR | NR | NS RPR vs. no RPR | NR | NR |  |
|  |  |  |  |  |  | No RPR (n=613) |  | 15 | NR | NR |  | NR | NR |  |
| Gori, 2008  19132241  Italy RECLOSE | 600mg LD and 75mg/day MD Clopidogrel + 325 mg aspirin | CEPI PFA-100 | Stent thrombosis or cardiac death (composite) |  |  | residual platelet reactivity RPR (n=133) |  |  | 40% (21-61%) sensitivity  83% (80-86%) specificity |  | For specificity, <0.01 vs. LTA-ADP and <0.0001 vs. LTA-collagen |  |  |  |
| Gori, 2008  19132241  Italy RECLOSE | 600mg LD and 75 mg/day MD Clopidogrel + 325 mg aspirin | CEPI PFA-100 among patients at high risk for AEs | Stent thrombosis or cardiac death (composite) |  |  | residual platelet reactivity RPR (n=238) |  | NA | 36% (17-55%) sensitivity  83% (80-86%) specificity |  | For sensitivity, p<0.01 vs. LTA-ADP  For specificity, p<0.0001 vs. LTA-ADP and p<0.0001 vs. LTA-collagen | NR | NR |  |
| Gori, 2008  19132241  Italy RECLOSE | 600mg LD and 75mg/day MD Clopidogrel + 325 mg aspirin | CADP PFA-100 among patients at high risk for AEs | Stent thrombosis or cardiac death (composite) |  |  | residual platelet reactivity RPR (n=196) |  | NA | 80% (55-100%) sensitivity  52% (46a -57%) specificity |  | For specificity, p<0.001 vs CEPI–PFA-100 | NR | NR |  |
| Gori, 2008  19132241  Italy RECLOSE | 600mg LD and 75mg/day MD Clopidogrel + 325 mg aspirin | CEPI PFA-100 | Stent thrombosis or cardiac death (composite) |  |  | residual platelet reactivity RPR |  |  | OR 3.24 | 1.42-7.38 | 0.003 logistic regression Univariate analysis | NR | NR |  |
| Gori, 2008  19132241  Italy RECLOSE | 600mg LD and 75mg/day MD Clopidogrel + 325 mg aspirin | CEPI PFA-100 | Stent thrombosis or cardiac death (composite) |  |  | residual platelet reactivity RPR |  | NR | OR 2.60 | 1.08-6.21 | 0.031 logistic regression Multivariate analysis |  | NR |  |
| Chiu 2011  21925055  Taiwan  NR | Clopidogrel (300 mg LD + 75 mg/d MD); Aspirin 100 mg/day or 300 mg LD + 100 mg/day | CADP PFA-100 | CV death, non-fatal MI, or non-fatal stroke |  | 24 months | CADP-CT<95s  (n=29) | MACE+ | 11 | HR =7.8 | 2.2-28.3 | 0.002 (<95s vs ≥ 95s  Log rank test | No | NR |  |
|  |  |  |  |  |  | CADP-CT≥95s  (n=105) | MACE+ | 3 |  |  |  |  |  |  |
|  |  |  |  |  |  | CADP-CT<95s  (n=29) | MACE+ | 11 | HR =5.28 | 1.37-20.08 | 0.015 (<95s vs ≥ 95s\_  Log rank test | Yes; Age,Male gender,CEPI-CT <193 s, diabetes mellitus, Hypertension, LV ejection fraction (%), creatinine (mg/dl), statins use, von williebrand aggregation % (natural log-transformed), acute coronary syndrome at admission | NR |  |
|  |  |  |  |  |  | CADP-CT≥95s  (n=105) | MACE+ | 3 |  |  |  |  |  |  |
|  |  |  | CV death, non-fatal MI, or non-fatal stroke plus hospitalization due to a cardiac ischemic event, including unstable angina and urgent target vessel revascularization (TVR) |  | 24 months | CADP-CT <95s  (n=29) | MACE+ | 27 |  |  | P<0.001 (<95s vs ≥ 95s  Log rank test |  |  |  |
|  |  |  |  |  |  | CADP-CT≥95s  (n=105) | MACE+ | 6 |  |  |  |  |  |  |

\*Myocardial infarction was defined as any typical rise and fall of cardiac markers in the setting of clinical signs or symptoms consistent with the new definitions of MI as described by the European Society of Cardiology. The academic research consortium definitions were used for stent thrombosis (definite, probable, and possible).